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Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Falls are a frequent and serious complication of Parkinson's disease and are related partly to an underlying cholinergic deficit that contributes to gait and cognitive dysfunction in these patients. Gait dysfunction can lead to an increased variability of gait from one step to another, raising the likelihood of falls. In the ReSPonD trial we aimed to assess whether ameliorating this cholinergic deficit with the acetylcholinesterase inhibitor rivastigmine would reduce gait variability.

Methods We did this randomised, double-blind, placebo-controlled, phase 2 trial at the North Bristol NHS Trust Hospital, Bristol, UK, in patients with Parkinson's disease recruited from community and hospital settings in the UK. We included patients who had fallen at least once in the year before enrolment, were able to walk 18 m without an aid, had no previous exposure to an acetylcholinesterase inhibitor, and did not have dementia. Our clinical trials unit randomly assigned (1:1) patients to oral rivastigmine or placebo capsules (both taken twice a day) using a computer-generated randomisation sequence and web-based allocation. Rivastigmine was uptitrated from 3 mg per day to the target dose of 12 mg per day over 12 weeks. Both the trial team and patients were masked to treatment allocation. Masking was achieved with matched placebo capsules and a dummy uptitration schedule. The primary endpoint was difference in step time variability between the two groups at 32 weeks, adjusted for baseline age, cognition, step time variability, and number of falls in the previous year. We measured step time variability with a triaxial accelerometer during an 18 m walking task in three conditions: normal walking, simple dual task with phonemic verbal fluency (walking while naming words beginning with a single letter), and complex dual task switching with phonemic verbal fluency (walking while naming words, alternating between two letters of the alphabet). Analysis was by modified intention to treat; we excluded from the primary analysis patients who withdrew, died, or did not attend the 32 week assessment. This trial is registered with ISRCTN, number 19880883.

Findings Between Oct 4, 2012 and March 28, 2013, we enrolled 130 patients and randomly assigned 65 to the rivastigmine group and 65 to the placebo group. At week 32, compared with patients assigned to placebo (59 assessed), those assigned to rivastigmine (55 assessed) had improved step time variability for normal walking (ratio of geometric means 0·72, 95% CI 0·58–0·88; p=0·002) and the simple dual task (0·79; 0·62–0·99; p=0·045). Improvements in step time variability for the complex dual task did not differ between groups (0·81, 0·60–1·09; p=0·17). Gastrointestinal side-effects were more common in the rivastigmine group than in the placebo group (p<0·0001); 20 (31%) patients in the rivastigmine group versus three (5%) in the placebo group had nausea and 15 (17%) versus three (5%) had vomiting.

Interpretation Rivastigmine can improve gait stability and might reduce the frequency of falls. A phase 3 study is needed to confirm these findings and show cost-effectiveness of rivastigmine treatment.

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Introduction

Falls are a common and devastating event in individuals with Parkinson's disease. Prospective studies report that 70% of people with Parkinson's disease have at least one fall in a year and 39% fall recurrently;[1] median survival in patients that have recurrent falls is 6 years.[2] Even in those who have not previously fallen, 21% will fall in the next 3 months.[3] Consequences of falls include fractures and injury,[4] fear of future falls,[5] hospital admission,[6] and increased caregiver burden,[7] with falls cited as one of the worst aspects of the disease.[8] Despite increased understanding of the pathophysiology that underlies risk of falls, few efficacious interventions are available. There is therefore an urgent and unmet need to identify effective treatment strategies.

Parkinson's disease is associated with slowing of gait due to reductions in step length[9] and a loss of gait automaticity, manifesting as increased gait variability.[9–11] Increased gait variability reflects impaired neural control of gait, in which large variation from one step to the next

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials with "Parkinson disease" and "cholinesterase inhibitors" as MeSH terms and without any language or date restrictions. We identified 20 studies, of which five reported a fall-related outcome. Only one randomised crossover trial sought to determine the effect of an acetylcholinesterase inhibitor, donepezil, on falls in Parkinson's disease (Chung et al, 2010). In this trial, 23 patients who reported falling or near-falling more than two times a week were given donepezil or placebo for 6 weeks and then crossed over. Donepezil treatment was associated with a reduction in fall rate from 0·25 falls per day on placebo to 0·13 falls per day on donepezil (p=0·49). However, frequent fallers drove the observed benefit and the finding was reported only in patients who had adhered to the protocol. The study was small and of short duration. Two randomised controlled trials of rivastigmine versus placebo reported falls as adverse events. Both reported lower proportions of falls occurring in the acetylcholinesterase inhibitor groups than in the placebo groups (seven [3%] of 211 *vs* nine [7%] of 123 patients; and 21 (6%) of 362 *vs* 11 (6%) of 179 patients), although in both studies the absolute numbers were small. One study reported that galantamine was associated with a decrease in falls, freezing, and gait domains of the Unified Parkinson's Disease Rating Scale. Another trial stated that "increased number of falls" contributed to withdrawal of a participant.

Added value of this study

To our knowledge, this is the first randomised controlled trial to examine the effect of rivastigmine on gait stability and falls in Parkinson's disease. Rivastigmine improved measures of gait stability and reduced fall frequency in people with Parkinson's disease without dementia. Rivastigmine is already licensed for Parkinson's disease dementia, hence its efficacy to enhance cognition is established, along with its tolerability and safety profile. Our trial design provides some insight into the mechanisms by which rivastigmine improves gait and reduces fall rates, and might inform future interventions and trial designs.

Implications of all available evidence

These findings support the role for acetylcholinesterase inhibitors in ameliorating gait dysfunction and fall prevention in Parkinson's disease. These findings need to be reproduced in a large phase 3 trial with falls as the primary outcome measure and that will collect evidence on cost-effectiveness.

results in a highly unstable gait and falls become more likely. Therefore, gait variability serves as a marker of fall risk in individuals with Parkinson's disease, as well as in those with Alzheimer's disease[12] and in older adults.[13] To compensate for the reduced gait stability, people with Parkinson's disease need additional attentional cognitive resource.[14,15] Higher demands on attention are made when negotiating complex walking environments or when walking while undertaking concurrent cognitive tasks. When attentional demands outweigh capacity, gait performance and ability to do concurrent tasks, or both, are impaired. Dysexecutive syndrome in Parkinson's disease[16] adds to this problem in that attentional resources are inappropriately prioritised away from gait and towards concurrent tasks.[17] Postural stability is therefore compromised in situations in which concurrent motor and cognitive demands compete for limited and impaired attentional resource; consequently falls occur.[18] Dual task paradigms that explore this cognitive-motor interface have revealed strong associations between gait variability and disease severity,[14,19] complexity of dual tasks,[20] cognitive deficits,[19,21] and history of falls.[10,11,22]

An underlying loss of cholinergic function contributes to freezing[23] and other gait changes, postural instability, and cognitive dysfunction.[24] The increasing importance of the role of the brainstem pedunculopontine nucleus (PPN) in gait and falls has been shown by neuroimaging,[25,26] lesioning,[27] and deep-brain stimulation studies.[28] Not only is Parkinson's disease associated with loss of cholinergic cell bodies in the PPN,[25] but also cholinergic output loss in the thalamus (the main target for cholinergic projection from the PPN) is greater in individuals who fall than in non-fallers.[26] Similarly, cholinergic loss in the nucleus basalis of Meynert, which projects to the cortex,[29] is purported to contribute to cognitive dysfunction in Parkinson's disease. The resultant impairment of attention affects the successful execution of complex motor behaviours; in rats a dual dopaminergic–cholinergic hit seems to confer propensity to falls during complex motor movement.[30] The cholinergic deficit that contributes to gait and cognitive dysfunction in Parkinson's disease provides a rationale on which to base and target drug treatment. We hypothesised that treatment with an acetylcholinesterase inhibitor would improve gait stability and therefore prevent falls in people with Parkinson's disease. Here we aimed to assess whether this hypothesis was correct in patients that had fallen in the last year.

Methods

Study design and participants

We carried out this randomised placebo-controlled, double-blind, parallel-arm, trial at North Bristol NHS Trust Hospital, Bristol, UK. The protocol has been published previously.[31] Patients were eligible if they had moderate (Hoehn and Yahr stage 2–3) idiopathic Parkinson's disease (diagnosed by a movement disorder specialist) and had been stable (no drug adjustments needed) on antiparkinsonian drugs for 2 weeks before enrolment. Patients were taking dopaminergic drugs, along with a wide range of drugs for comorbidities.

Patients had to demonstrate the ability to walk 18 m without a walking aid and had to have reported at least one fall in the previous year; the best predictor of future falls.[3] Patients were excluded if they did not speak English; had an absolute contraindication to, or had previously taken, acetylcholinesterase inhibitors; or had any other neurological, visual, or orthopaedic problem that meaningfully interfered with gait. We excluded patients with dementia, classified using the Movement Disorder Society Task Force definition of decreased cognition of sufficient severity to impair daily life.[32]

We recruited participants from community and hospital settings in the UK (mostly in southeast England). Patient Identification Centres were set-up to identify patients in other local centres and Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) nurses did pre-screening of potential participants in hospital clinics. We also recruited participants from the Parkinson's Register of the Dementias and Neurodegenerative Diseases Research Network (ProDeNDRoN) database and the trial recruitment details were publicised via the Parkinson's UK charity research network and local media. All participants gave written informed consent.

Ethics approval was granted by the South West Research Ethics Committee on Sept 28, 2011, and a Clinical Trial Authorisation granted from the Medicines and Healthcare Regulatory Agency (MHRA) on June 18, 2012.

Randomisation and masking

Patients were randomly assigned (1:1) to oral rivastigmine or placebo capsules matched to those for rivastigmine in colour and weight. We intended to randomise using a minimisation approach; however, during recruitment and while assignments remained blinded, it became apparent that a technical problem with the randomisation system (human error) had led to participants being randomised using simple randomisation. We therefore chose to continue with simple randomisation because the anticipated sample size (>100 people) would most likely result in balance between known and unknown confounders. Participants were enrolled and tested by an investigator who had no access to the randomisation sequence, which was computer generated by the Bristol Randomised Trials Collaboration (BRTC) clinical trials unit using a web-based program and accessed by the research team via a secure webpage. A treatment pack number was issued via a secure website that matched the number to a drug pack held in the pharmacy to ensure concealment of allocation. We assessed whether participants were aware of their treatment group status by asking them at the 32 week follow-up visit to guess which treatment they had received.

Procedures

A full description of the assessments used in the trial is in the published protocol.[31] Baseline measures of general health status and sociodemographics were recorded by EJH. We assessed gait and balance, cognition, mood, and fall risk factors at baseline (pre-treatment) and at the end of the 32 week treatment period. We measured occurrence of falls with use of monthly falls diaries, which patients posted monthly to the investigators. We telephoned participants every month to corroborate fall information, titrate medication, and to record adverse events. Our methods were consistent with guidelines from the Prevention of Falls Network Europe,[33] which recommend "prospective daily recording and a notification system with a minimum of monthly reporting" and the use of telephone interviews for verification.

For assessment of the primary endpoint, participants were asked at the baseline and 32 week visit to walk along a 22 m, flat, outdoor, covered walkway while wearing a triaxial accelerometer (DynaPort Hybrid, McRoberts, Netherlands). Patients were assessed in the on-drug state in repect to their standard dopaminergic drugs. The middle 18 m, marked by external triggers, was used to assess steady state walking performance. We used three conditions: normal walking, simple dual task with phonemic verbal fluency (walking while naming words beginning with a single letter), and complex dual task switching with phonemic verbal fluency (walking while naming words, alternating between two letters of the alphabet). Each condition was done three times, yielding nine walks in total, to ensure accurate assessment of gait performance. Using a computer-generated random list generated by BRTC we randomly ordered the conditions to minimise fatigue and practice effects. Gait analysis used accepted standards known to be sensitive to both a diagnosis of Parkinson's disease[34] and predictive of falls.[35]

For more about **DeNDRoN** see https://www.crn.nihr.ac.uk/dementia

Rivastigmine (or equivalent as placebo) dose was started at 3 mg per day (1·5 mg tablet taken twice a day) and was uptitrated in 3 mg per day (or placebo) increments every 4 weeks to a maximum of 12 mg per day at week 13 onwards. Participants were given sufficient capsules of all four strengths (1·5 mg, 3 mg, 4·5 mg and 6 mg rivastigmine or matched placebo) for the study period and were advised on which to take by the trial team (overseen by EJH) via telephone. Identical titration was performed for those taking placebo to maintain masking. The highest tolerated dose was maintained for the following 16 week period, yielding a total treatment period of 32 weeks. Participants were instructed to downtitrate to the last tolerated dose or stop the drug, which was decided according to clinical judgment when unacceptable side-effects occurred.

Surveillance for adverse events took place over 12 months, which included the 4 months beyond the intervention period to detect any events with a prolonged latency. Patients were provided with a leaflet detailing potential side-effects and could telephone the study team to report adverse events at any time. Blinded researchers

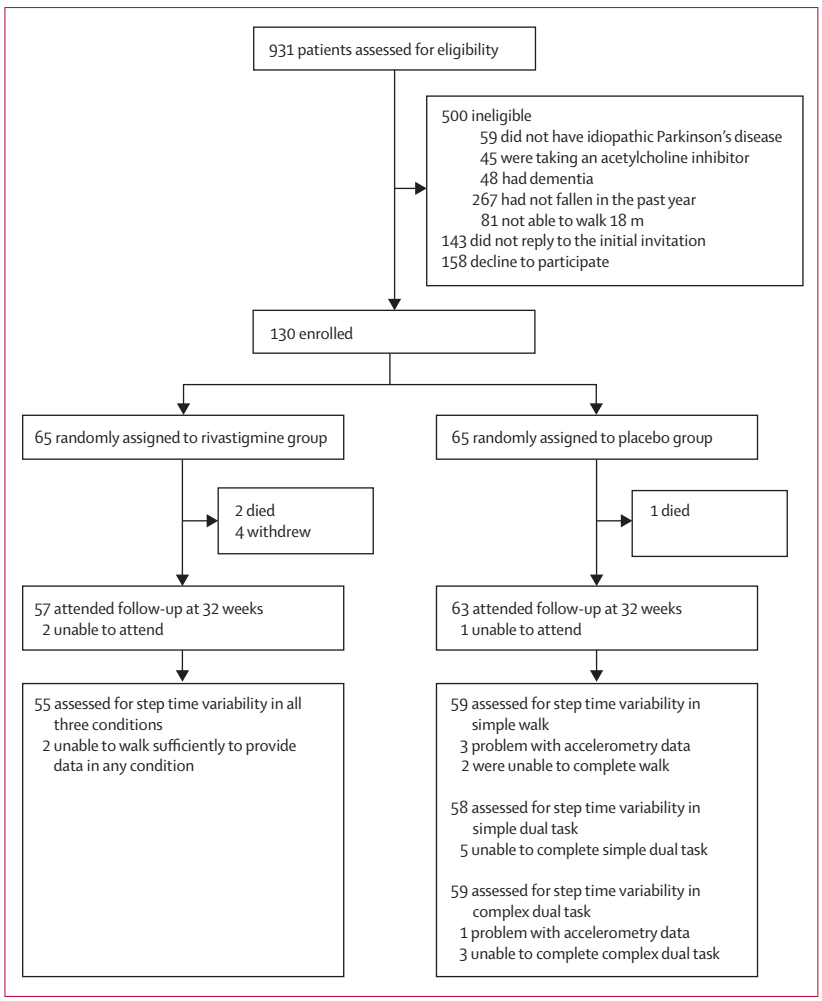

Figure 1: **Trial profile**

See Online for appendix

established seriousness, causality, intensity, expectedness, and severity of adverse events according to established criteria[36] and events were coded post hoc using the MedDRA dictionary, version 17.1.

Outcomes

The primary outcome was difference in step time variability between the two groups at 32 weeks and adjusted for baseline age, cognition, step time variability, and number of falls in the previous year. Secondary outcomes were the rate per month of falls defined as an unexpected event in which participants come to rest on the ground, floor, or lower level,[33] and functional mobility through gait speed in each condition (time taken to walk the 18 m). Other pre-specified secondary outcomes were fall risk (Physiological Profile Assessment falls risk score); fear of falling (short-form Iconographical Falls Efficacy Scale [ICON-FES] total score); controlled leaning balance; episodes of freezing of gait in the past month; cognition and mood (Montreal Cognitive Assessment [MoCA] total score, Frontal Assessment Battery total score, Geriatric Depression Scale (GDS-15) total score, and Cognitive Failures Questionnaire total score); disease severity (via Movement Disorder Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS] total score); levodopa dose;[37] and quality of life (measured by EuroQol's EQ-5D-5L and described in the visual analogue score and index score, derived using Office of Health Economics UK value set[38]).

Statistical analysis

We had little evidence to guide the power calculation since no data were available on the effect of rivastigmine on step time variability. A sample size of 130 was chosen on the basis of an anticipated 30% drop-out rate,[39] resulting in about 90 patients (45 per arm). This sample size would enable a treatment effect difference of 0·6 standardised (*Z* score) units for the primary outcome measure to be detected with 80% power and at a two-sided 5% significance level. This sample size was similar to that used in a study of patients without Parkinson's disease but with mild cognitive impairment.[40]

Gait variability was assessed using the SD of step times. We established step time from consecutive heel strike peaks in the acceleration trace. We calculated the SD of step times for each walk and used the mean of these SDs across all three walks, for each condition, as the primary endpoint of step time variability in the statistical analysis. We specified the SD of step times and not the SD of stride times because it includes assessment of within-stride gait asymmetry in people with Parkinson's disease and provides more data points, which enables more reliable measurement of gait variability (appendix).[41]

The primary analysis was done in a modified intention-to-treat population, whereby we included all patients except those who withdrew, did not attend assessment, or died. Secondary analyses were done in participants in the modified intention-to-treat population from whom data were available. Adverse event and safety analyses were done in the full trial population.

When outcomes were positively skewed (primary outcome included) we log-transformed the outcome, hence the coefficients from our models represent the proportional change (geometric ratio means) in outcome between the treated and placebo groups. The percentage reduction was calculated by 100−geometric ratio mean. When transformation could not achieve normality, we categorised data and used ordinal logistic regression models. We used multivariable linear models to adjust for a-priori specified determinants of gait variability measured at baseline (centred around the mean if appropriate); age, cognitive function (MoCA), previous falls (ordinal variable 1, 2–3, 4–6, 7–19, ≥20) and baseline log step time variability.

For the primary outcome, we did pre-specified subgroup analyses for age group, cognitive function (MoCA), and Parkinson's disease duration, measured as time in years from onset of first motor symptom to enrolment, by fitting interaction terms to the

multivariable regression models. We made no formal correction for multiple testing. We used negative binomial regression for the analysis of fall rates as recommended,[42] because these data are known to cluster within individuals and an initial exploratory model using Poisson regression confirmed that the data were over-dispersed. We used the same covariates as for the primary outcome analysis for the falls analysis. Where data could not be transformed to meet the assumptions of normality it was categorised (appendix). We use descriptive statistics to report adverse events from all patients, irrespective of medication and protocol adherence. A planned sensitivity analysis of the primary outcome was done with use of multiple imputation for missing data. All analyses were done with Stata version 13.1.

We did not convene a data monitoring committee because rivastigmine is in widespread use. However, an independent advisor (a clinical academic) was appointed to review all serious adverse events (unblinded if necessary) and advise the trial team. The trial was registered with ISRCTN, 19880883; WHO universal trial number U1111–1124–0244.

Role of the funding source

The funder (Parkinson's UK) had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Novartis provided feedback about the dosing of the trial drug, but had no other input into the design or implementation of the study and did not participate in preparing this manuscript for publication. The corresponding author had full access to all the data and had final responsibility to submit for publication.

	Placebo (n=65)	Rivastigmine (n=65)
Median age (range)	69 (46–88)	71 (54–90)
Men	46 (71%)	35 (54%)
Women	19 (29%)	30 (46%)
Falls and gait measures		
Number of falls in previous year	5·5 (2·0–12·5)	5·0 (2·0–12·0)
Gait speed (m/s)	1·0 (0·3)	1·0 (0·3)
Step time variability (s)		
Normal walk	0·024 (0·018–0·039)*	0·026 (0·020–0·047)
Walk plus simple cognitive task	0·049 (0·030–0·110)	0·053 (0·028–0·138)
Walk plus complex cognitive task	0·068 (0·036–0·149)	0·078 (0·035–0·167)
Have experienced freezing of gait in previous month	48 (74%)	42 (65%)
Total freezing of gait score if experienced a freezing	15·8 (3·9)†	15·3 (4·8)
ICON-FES (fear of falling)	24·0 (5·17)	22·9 (6·72)
PPA falls risk score	1·9 (1·4)	1·9 (1·9)
Controlled leaning balance	22 (16–32)‡	17 (10–26)§
Cognitive measures		
Montreal Cognitive Assessment	26 (23–27)	24 (22–27)
Frontal Assessment Battery	14 (12–16)	15 (12–16)
Geriatric Depression Scale	3 (2–6)	3 (1–5)
Cognitive Failures Questionnaire	41 (30–48)	39 (30–47)
Disease measures		
MDS-UPDRS	90 (74–106)	87 (64–99)
Levodopa equivalent dose (mg)	980 (650–1298)	710 (450–1075)
Duration of Parkinson's disease (years)	9 (5–13)	8 (5–13)*
Quality-of-life EQ-5D-5L visual analogue score	65 (17)	64 (17)
Quality-of-life EQ-5D-5L index score	0·705 (0·18)	0·718 (0·19)

Data are n (%), median (IQR), or mean (SD), unless otherwise specified. ICON-FES=Iconographical Falls Efficacy Scale. PPA=Physiological Profile Assessment. MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale. LED=levodopa equivalent dose. *n=64. †n=45. ‡n=58. §n=50.

Table 1: **Baseline demographic and clinical characteristics**

Results

Between Oct 4, 2012, to March 28, 2013, we enrolled 130 patients, randomly assigning 65 to the rivastigmine group and 65 to the placebo group (figure 1). Baseline demographic and clinical characteristics were similar between groups, although there were more women in the rivastigmine group and the daily levodopa equivalent dose was higher in the placebo group (table 1). Of the 130 participants enrolled, three died, four withdrew, and three were too unwell to attend the 32 week assessment. One additional participant provided some verbal outcome data via telephone.

We assessed 59 patients in the placebo group and 55 in the rivastigmine group for step time variability; some patients were excluded from certain conditions because they were unable to complete the walk or because of problems with the accelerometry data (figure 1). Step time variability was 28% lower (geometric mean ratio 0·72, 95% CI 0·58–0·89; p=0·002) in the normal walking task and 21% lower (0·79, 0·62–0·99; p=0·045) during the simple dual task in those assigned to rivastigmine compared with those assigned to placebo (table 2). The 19% improvement in step time variability shown in the rivastigmine group during the complex dual task was not significant (0·81, 0·60–1·09; p=0·17). There was no evidence of any effect modification with age, cognition, or disease duration in any of the three walking conditions (all interaction p>0·05), although we recognise that these analyses were probably underpowered to detect a difference. In a sensitivity analysis with multiple imputed datasets for missing data (appendix) the results for normal walking became more conservative (geometric mean ratio 0·77, 95% CI 0·61–0·97; 0·027) and the difference between the groups in the simple dual task was no longer significant (0·84, 0·65–1·07; p=0·15).

One participant in the rivastigmine group had an extremely high number of falls (1122 falls during the treatment period) and so was removed from the analysis of fall rate. Median fall rate in the rivastigmine group (n=64; one outlier excluded) was 0·50 (IQR 0·14–0·89), compared with 1·14 (0·27–2·6) in the placebo group (n=65; figure 2). After adjustment for age, baseline cognition (MoCA score), falls in the previous year

	Placebo group (n=59)	Rivastigmine group (n=55)	Unadjusted GMR (95% CI)	Adjusted* GMR (95% CI)	SE	p value	Reduction (%)
Normal walk†	0·064 s (0·114); 0·027 s (0·019–0·054)	0·043 s (0·044); 0·023 s (0·016–0·049)	0·83 (0·60–1·15)	0·72 (0·58–0·89)	0·076	p=0·002	28%
Simple cognitive task plus walk†	0·122 s (0·231); 0·060 s (0·034–0·114)	0·111 s (0·199); 0·042 s (0·025–0·145)	0·85 (0·59–1·23)	0·79 (0·62–0·99)	0·093	p=0·045	21%
Complex cognitive task plus walk	0·161 s (0·238); 0·078 s (0·040–0·162)	0·145 s (0·221); 0·065 s (0·031–0·167)	0·86 (0·58–1·27)	0·81 (0·60–1·09)	0·122	p=0·17	19%

Data for step time variability given in seconds (s) and are mean (SD); median (IQR). *Adjusted for centred age, centred baseline cognition (MoCA score), centred log baseline step time variability of condition, and previous falls categorised as (1, 2–3, 4–6, 7–19, ≥20). †n=58 for placebo group. GMR=Geometric mean ratio.

Table 2: **Step time variability at 32 weeks (primary outcome)**

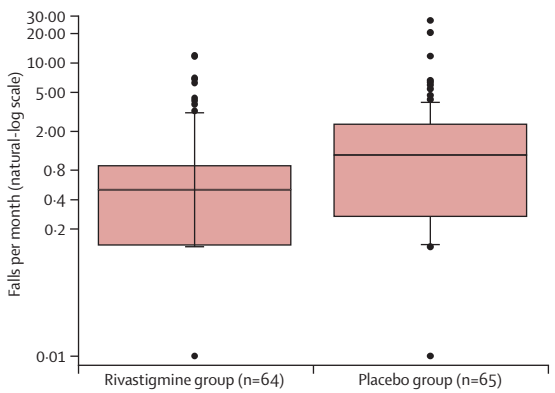

Figure 2: **Crude fall rate by treatment group**
Box and whisker plot shows median (line) and IQR (box); upper and lower whiskers represent the 15th to 85th centiles. Values above and below whiskers plotted separately (dots), but we excluded one extreme outlier. 18 participants (nine in each group) had a fall rate of zero and were assigned an arbitrary value of 0·01 on the log scale; dots for these participants are superimposed.

(quintiles 1, 2–3, 4–6, 7–19, ≥20), and baseline step time variability during normal walking, participants in the rivastigmine group had a reduction of 45% in the rate of falls per month (table 3). We did two post-hoc sensitivity analyses to account for exclusion of the outlier from the calculation of fall rate. We repeated the negative binomial regression model but including the outlier, who was assigned the next highest value of falls (number of falls plus one of next highest participant in that group). The adjusted difference in fall rate remained significant (incident rate ratio 0·58, 95% CI 0·58–0·85; p=0·005; appendix). Using multinomial logistic regression, fall rates were categorised as low, intermediate, high, or very high, with the outlier in the very high category (appendix). Treatment with rivastigmine was associated with a reduced chance of being in the high fall rate or very high fall rate categories compared with the low fall rate category (appendix). On visual inspection, fall rates increased over time in the placebo group, but not in the rivastigmine group (figure 3).

Rivastigmine was associated with a small but significant improvement in gait speed in all three task conditions, with the greatest effect seen in normal walking (table 3). Improvements in controlled leaning balance were present in the rivastigmine group (more people in the rivastigmine group belonged to the low score group [good performance] *vs* medium and high score groups [poorer performance]; table 3). All other secondary outcomes—ie, fall risk, fear of falling, freezing of gait in the past month, cognition and mood measures, disease severity, levodopa requirement, and quality of life measures—did not differ between patients assigned to rivastigmine and those assigned to placebo (table 3).

At 32 week follow-up or withdrawal, 39 (60%) of 65 participants in the rivastigmine group versus 46 (71%) of 65 participants in the placebo group were still taking the study drug. Three participants in the rivastigmine group stopped for reasons not related to adverse events (participant choice, n=2; additional drug started that was contraindicated with rivastigmine, n=1); all other stoppages (n=23 in rivastigmine group, n=19 in placebo group) were due to adverse events. At 32 weeks, participants in the placebo group were taking a higher median treatment dose per day (10·0 mg, IQR 6·0–10·5) than were those in the rivastigmine group (6·3 mg, 2·7–8·7).

We did a post-hoc analysis to assess masking success using Bang's Blinding Index.[43] The null value of the Bang Blinding Index is 0, with a value greater than 0 representing failure in masking and a value lower than 0 suggesting that the failure in blinding is reversed. Bang's blinding index was 0·6 (95% CI 0·8–0·3) for the rivastigmine group and 0·2 (95% CI 0·4–0·0) for the placebo group, indicating that more participants in the rivastigmine group guessed their allocation correctly than would be expected by chance.

During the treatment period, 2184 adverse events occurred, of which 1875 were falls (1197 falls in placebo group, 678 falls in rivastigmine group). 27 adverse events were classified as serious (14 in the rivastigmine group and 13 in the placebo group; appendix). Of the 14 serious adverse events that occurred in the rivastigmine group, only two were assessed as being probably or definitely related to the treatment, both of which were worsening of parkinsonism. About a third of participants in the rivastigmine group experienced nausea (n=20 [31%]; table 4), which was similar to the reported frequency of nausea with rivastigmine in a larger clinical trial.[39] Nearly

	Placebo group	n	Rivastigmine group	n	Unadjusted difference between groups (95% CI)	Adjusted difference* between groups (95% CI)	p value
Falls							
Falls per month	2·4 (4·40)	65	1·4 (2·47)	65	0·60† (0·37–0·96)	0·55† (0·38 to 0·81)	0·002
PPA falls risk score	2·2 (2·0)	63	2·2 (1·1)	57	0·95‡ (0·65 to 1·38)	0·97‡ (0·67 to 1·39)	0·85
Fear of falling (ICON-FES)	24·9 (5·6)	63	23·8 (7·9)	58	–1·10‡ (–3·55 to 1·36)	–0·25‡ (–2·03 to 1·53)	0·78
Gait speed (m/s)							
Normal walk	0·99 (0·33)	58	1·08 (0·29)	55	0·08§ (–0·03 to 0·20)	0·11§ (0·04 to 0·18)	0·003
Walk plus simple cognitive task	0·74 (0·30)	58	0·79 (0·33)	55	0·05§ (–0·07 to 0·17)	0·08§ (0·00 to 0·16)	0·037
Walk plus complex cognitive task	0·66 (0·29)	59	0·71 (0·32)	55	0·05§ (–0·06 to 0·17)	0·08§ (0·00 to 0·16)	0·048
Controlled leaning balance score							
Low (good performance)	7 (12%)	58	18 (36%)	50	Ref	Ref	..
Medium	17 (29%)	58	12 (24%)	50	0·27¶ (0·09 to 0·86)	0·11¶ (0·02 to 0·57)	0·008
High	19 (33%)	58	8 (16%)	50	0·16¶ (0·05 to 0·54)	0·08¶ (0·01 to 0·53)	0·009
Very high (poor performance)	15 (26%)	58	12 (24%)	50	0·31¶ (0·10 to 1·00)	0·19¶ (0·03 to 1·26)	0·085
Freezing							
FOG episode in past month	48 (76%)	63	36 (63%)	57	0·54‖ (0·24 to 1·18)	0·46‖ (0·13 to 1·60)	0·22
New freezing of gait score if history of freezing	16·1 (4·4)	48	15·8 (4·4)	34	–0·29‡ (–2·25 to 1·67)	0·34‡ (–1·11 to 1·79)	0·64
Cognitive and mood measures							
Cognition (MoCA score)	24·3 (3·8)	63	24·1 (3·9)	57	1·01‡ (0·93 to 1·09)	0·99‡ (0·93 to 1·06)	0·78
Executive function (Frontal Assessment Battery score)	14·2 (3·3)	63	14·6 (2·7)	57	0·95‡ (0·78 to 1·15)	0·95‡ (0·81 to 1·12)	0·57
Mood (Geriatric Depression Scale score)	4·7 (3·0)	63	5·0 (3·7)	58	1·00‡ (0·80 to 1·24)	0·98‡ (0·80 to 1·19)	0·83
Cognitive failures questionnaire score	38·9 (14·6)	63	40·3 (14·2)	58	1·40§ (–3·79 to 6·59)	1·90§ (–1·28 to 5·09)	0·24
Disease measures							
MDS-UPDRS	95·5 (28·2)	63	87·2 (29·7)	57	–8·28§ (–18·76 to 2·20)	–3·29§ (–9·59 to 3·02)	0·30
Levodopa requirement							
Very low (<550 mg per day)	10 (17%)	59	18 (33%)	55	Ref	Ref	..
Low (551–889 mg per day)	16 (27%)	59	12 (22%)	55	0·42¶ (0·14 to 1·22)	1·42¶ (0·26 to 7·79)	0·68
Moderate (900–1244 mg per day)	14 (24%)	59	15 (27%)	55	0·60¶ (0·21 to 1·72)	5·20¶ (0·63 to 42·81)	0·13
High (≥1245mg per day)	19 (32%)	59	10 (18%)	55	0·29¶ (0·10 to 0·87)	2·22¶ (0·19 to 26·06)	0·53
Quality of life							
Quality of life (EQ-5D-5L) Index score	0·663 (0·19)	63	0·657 (0·21)	58	–0·006§ (–0·078 to 0·066)	0·007§ (–0·051 to 0·066)	0·82
Quality of life (EQ-5D-5L) VAS score	63 (18)	63	66 (16)	58	3·7§ (–2·5 to 10·0)	5·5§ (–0·2 to 11·2)	0·058

Outcome data are mean (SD) or n (%). MoCA=Montreal Cognitive Assessment. VAS=visual analogue score. PPA=Physiological Profile Assessment. MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale. ICON-FES=Iconographical Falls Efficacy Scale. FOG=freezing of gait. *Adjusted for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2–3, 4–6, 7–19, ≥20). †Incidence rate ratio (negative binomial regression model). ‡Geometric mean ratio. §Mean difference. ¶Relative risk ratio. ||Odds ratio.

***Table* 3: Secondary outcomes**

three-times more participants assigned to rivastigmine (11 [17%]) than to placebo (n=3 [15%]) had vomiting. Most adverse events were considered to be mild (1175 [89%] of 1319 events in rivastigmine group; 663 [77%] of 865 events in placebo group) and unrelated to the interventions (778 [90%] of 865; 1302 [99%] of 1319). Three deaths occurred; all were unrelated to the trial drug—one patient each died from known malignancy, peritonitis, and previously unknown pancreatic malignancy. No adverse events that we considered to be related to the study drug occurred between end of the treatment period and the 52 week follow-up.

Discussion

To our knowledge, this is the first trial to show that rivastigmine can improve gait stability and might reduce falls in patients with Parkinson's disease, and has acceptable tolerability and safety consistent with previous work. Because we did not adjust for multiple testing, the beneficial effect on step time variability for the simple cognitive task should be interpreted with caution and a sensitivity analysis with an imputed dataset rendered this association not significant.

Different strategies have been trialled to reduce fall risk in Parkinson's disease. Consensus-based

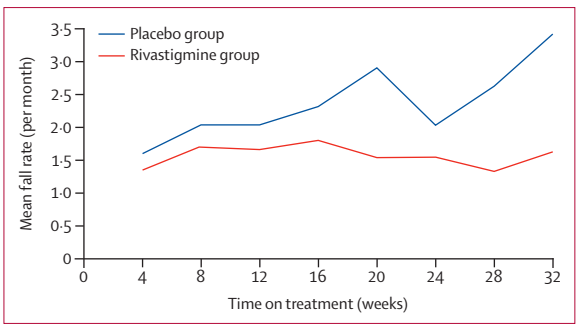

Figure 3: **Falls per month**

	Placebo (n=65)		Rivastigmine (n=65)	
	Participants (%)	Events	Participants (%)	Events
Cardiac disorders	4 (6%)	4	1 (2%)	1
Endocrine disorders	0	0	1 (2%)	1
Eye disorders	2 (3%)	2	2 (3%)	2
Gastrointestinal disorders*	12 (18%)	14	34 (52%)	55
Constipation	3 (5%)	3	1 (2%)	1
Diarrhoea	0	0	5 (8%)	5
Dyspepsia	1 (2%)	1	3 (5%)	3
Nausea	3 (5%)	3	20 (31%)	24
Salivary hypersecretion	2 (3%)	2	4 (6%)	5
Vomiting	3 (5%)	3	11 (17%)	15
General disorders and administration site disorders	6 (9%)	6	6 (9%)	7
Immune system disorders	0 (0%)	0	1 (2%)	1
Infections and infestations	4 (6%)	4	11 (17%)	15
Rhinitis	1 (2%)	1	3 (5%)	3
Urinary tract infections	0 (0%)	0	4 (6%)	5
Viral infection	0 (0%)	0	1 (2%)	1
Injury, poisoning, and procedural complications	4 (6%)	4	0 (0%)	0
Investigations	2 (3%)	2	3 (5%)	5
Metabolism and nutrition disorders	0	0	1 (2%)	1
Musculoskeletal and connective tissue disorders	5 (8%)	5	5 (8%)	7
Back pain	0	0	3 (5%)	3
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (2%)	1	1 (2%)	1
Nervous system disorders	35 (54%)	51	44 (68%)	71
Dizziness	6 (9%)	7	14 (22%)	17
Parkinsonism†	23 (35%)	29	28 (43%)	39
Psychiatric disorders	5 (8%)	6	8 (12%)	8
Renal and urinary disorders	4 (6%)	5	3 (5%)	3
Respiratory, thoracic, and mediastinal disorders	4 (6%)	4	4 (6%)	4
Skin and subcutaneous tissue disorders	5 (8%)	6	2 (3%)	3
Surgical and medical procedures	4 (6%)	5	2 (3%)	2
Vascular disorders	3 (5%)	3	0	0
Orthostatic hypotension	3 (5%)	3	0	0

MedDRA preferred term listed. *p<0·001 for difference between groups †Parkinsonism refers to worsening of pre-existing parkinsonism symptoms

Table 4: **Adverse events in at least three people, with the exception of falls**

recommendations to reduce fall risk were published in 2014 but with a small evidence base.[44] Acknowledging the multifactorial aetiology of falls, guidance advocates targeting interventions at age-specific and disease-specific risk factors. Early trials of physiotherapy based interventions were hampered by inadequate power and heterogeneity of the intervention delivered. However, trials of strength, balance, and cueing therapy in early disease[45] and of Tai chi[46] have shown significant reductions in fall rates (69% and 67%, respectively). The effect of deep-brain stimulation on gait, balance, and falls has produced conflicting results.[47] Extrapolation of results from these studies is limited by the small sample sizes, different targets, and the insufficient detail involved in reporting falls outcomes from the Unified Parkinson's Disease Rating Scale (UPDRS) part 2 item. Acetylcholinesterase inhibitor treatment with donepezil was shown to reduce falls frequency in a cross-over trial of 23 patients.[48] Although this effect appears to be driven by individuals who fell most frequently, this result is congruent with our findings and supports the potential role for acetylcholinesterase inhibitors in decreasing falls in Parkinson's disease.

The benefit of rivastigmine treatment on falls is likely to have resulted from improvement in gait variability, velocity, and balance. This gain might or might not be mediated via improved cognition, specifically improved attention to compensate for impaired gait resulting from striatal dopaminergic loss, or via a direct effect on gait.[27,30] Future analysis is needed to assess the mechanism of cognitive–gait interference, especially whether acetylcholinesterase inhibitor treatment ameliorates loss of attentional resource or whether it refocuses attentional priority to gait and movement control.[49] The apparent absence of significant improvement in the secondary measures of cognitive and executive function could have resulted from insensitivity of the measurement instruments in our population, which was not cognitively impaired. Additionally, these findings might have been a type 2 error because previous randomised controlled trials that have showed a benefit at treating patients with Parkinson's disease dementia were much larger in size.[39]

The high number of adverse events in both groups likely reflects the high burden of comorbidity seen in our older cohort, coupled with the fact that patients were primed and screened monthly for adverse events. The observed profile of adverse events is similar to that shown in previous reports and only a small proportion of the total events were likely to be related to the intervention. In future, administration of rivastigmine via patches, as is common in current clinical practice for Parkinson's disease dementia, might improve tolerability because use in Alzheimer's disease dementia is associated with lower rates of nausea and vomiting than with oral administration.[50] The occurrence of drug side-effects or positive outcomes for the actively treated group is likely to account for the observations that participants

in this group were more likely to correctly guess their allocation than would be expected by chance.

The strengths of this trial include its randomised placebo-controlled design, objective outcome measure, and high retention rate of participants. Because this was a phase 2 study, we choose a surrogate marker of fall risk, gait variability, because we were uncertain as to whether the trial would be sufficiently powered to detect a difference in fall rate, a more commonly used clinical outcome. Despite our double-blind design, there was some evidence that participants in the treatment group might have guessed allocation group and this might have biased our results. Use of acetylcholinesterase inhibitors for gait and balance might not be effective for all patients with Parkinson's disease. In excluding those who were dependent on walking aids, we might have excluded people with more marked gait dysfunction who would have had potentially greater benefit from the intervention. Alternatively, efficacy might be attenuated by the greater cholinergic deafferentation present in patients with more advanced disease. The single-site nature of the trial might also decrease the generalisability of these findings. Future studies with larger sample sizes will allow analyses to identify subgroups of patients that will benefit most from rivastigmine.

We believe it is now necessary to undertake a larger phase 3 randomised controlled trial with falls as the primary outcome and with a cost-effectiveness analysis before we can confidently advise on the routine use of rivastigmine in the management of falls in patients with Parkinson's disease.

Contributors

EJH, SRL, JCTC, ALW, YB-S, and ADL designed the study. Clinical care in the trial was performed by EJH and ALW. EJH, DMG, MAB, and YB-S did the analysis. EJH wrote the first draft. All authors read and approved the final manuscript.

Declaration of interests

SRL declares that the FallScreen fall risk assessment tool is commercially available through Neuroscience Research Australia (NeuRA); any profits from sales of the assessment are shared equally between the inventor (SRL), the falls and balance research group at NeuRA, and the NeuRA central fund. All other authors declare no competing interests.

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